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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/580,589	ROGUEDA, PHILIPPE	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 11-13* is/are pending in the application.

4a) Of the above claim(s) *10 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/1/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-7 and 10-13 are pending. Claim 10 is withdrawn as being drawn to non-elected invention. Claim 13 is withdrawn as being drawn to non-elected species. Claims 11-13 are new. Applicant amended claims 5-6 and 10. **Claims 1-7 and 11-12 are under consideration in the instant office action**. Receipt and consideration of Applicant's amended claim set, amended specification, replacement Figure 3, new IDS, and remarks/arguments submitted on February 1, 2010 are acknowledged. All rejections/objections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments and/or persuasive arguments.

Election/Restrictions

The restriction requirement and species election, first mailed on October 1, 2009, are maintained at this time. Applicant's confirmation of their telephonic election of Group I (a drug formulation comprising (i) HFA, (ii) partially or fully acylated cyclodextrin, and (iii) drug) and budesonide as the elected species is acknowledged. Newly submitted claims 11 and 13 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Applicant's previous election of formulations where the active agent is budesonide is distinct from formulations where the active agent is formoterol fumarate alone (claim 11) or a combination of (i) fluticasone propionate and salmeterol xinafoate (claim 13), (ii) ciclesonide and formoterol fumarate (claim 13), (iii) mometasone furoate and formoterol fumarate dihydrate (claim 13), or (iv) fluticasone propionate and formoterol fumarate dihydrate.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 11 and 13 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. New claims 11 and 13 do not recite budesonide as the drug or as one of the drugs in a combination of drugs. **Upon further consideration claims 7 and 11 are rejoined to the claims under examination**, because the prior art of record teaches formoterol fumarate dihydrate alone or in combination with budesonide.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-7 and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller et al. (WO 2003/066031) in view of Uekama et al. ("Cyclodextrin Drug Carrier Systems," *Chem. Rev.* 1998, *98*, pp 2045, 2048 (Table 2); and 2063), wherein US 2005/0085445 is being used as the English language equivalent of WO 2003/066031. All citations to Muller are to the English equivalent US publication.

Applicant Claims

Applicant claims a pharmaceutical composition comprising (i) any HFA (hydrofluoroalkane), (ii) a drug (dependent claim 6 limits the drug to those selected from a Markush group consisting of various drugs, including the elected drug, budesonide, and (iii) a partially or fully acylated alpha-, beta-, or gamma-cyclodextrin.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Muller teaches stabilized pharmaceutical **HFA suspension formulations** comprising (i) at least one pharmaceutical ingredient (e.g. **budesonide**), (ii) at least one propellant (e.g. HFA 227 or HFA 134a), (iii) **a native or modified alpha-, beta-, or gamma-cyclodextrine (e.g. hydroxypropyl-beta-cyclodextrine)**, and (iv) at least one hydrophilic additive (e.g. PEG or PVP) (title, abstract; [0014]-[0023]. Muller's preparation of the formulations involves **dissolving components (i) and (iii)-(iv) by mixing with ethanol** ([0029]). The solution formulation is transferred into a pressure-resistant container fitted with a metering valve and the suspension is formed upon addition to the solution formulation of the HFA propellant ([0029]-[0041]). Muller exemplifies the preparation of invented formulations wherein **the only drug is**

budesonide (Example 3: [0034]); the only drug is formoterol fumarate dihydrate (Example 4: [0035]); the only drug is salmeterol xinafoate (Example 8: [0039]); the only drug is fluticasone-17-propionate (Example 6: [0037]), and wherein the formulation comprises a combination of budesonide and formoterol fumarate dihydrate (Example 5: [0036]). Muller teaches that combinations **of active agents are also suitable** ([0022] and claim 3).

Uekama teaches that the most common pharmaceutical application of cyclodextrins is to enhance solubility, stability, and bioavailability of drug molecules, and that natural cyclodextrins generally exhibit poor water solubility (pp 2045). A variety of cyclodextrin derivatives are reported by Uekama and described in pharmaceutical applications, **including peracylated cyclodextrins, such as 2,3,6-tris-O-acetylcyclodextrin, 2,3,6-tri-O-hexanoylcyclodextrins, 2,3,6-tri-O-valerylcyclodextrins, etc.** (pg. 2047, Table 1; pg. 2048, Table 2, left column). The solubility behavior of various peracetylated-cyclodextr0ins in ethanol/water mixtures from 0% v/v ethanol to 100% v/v ethanol is depicted in Figure 2 on page 2048. **Compared to beta-cyclodextrin all but one of the peracylated cyclodextrins depicted in Figure 2 exhibited greater solubility in 100% ethanol**. Uekama also teaches **various peracylated cyclodextrins as being suitable to obtain prolonged-release pharmaceutical formulations** (pg. 2063, right column).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Muller lacks the teaching of formulations comprising partially or fully acylated cyclodextrins. This deficiency is cured by the teachings of Uekama.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to modify the teachings of Muller and utilize peracylated cyclodextrins in lieu of or in addition to hydroxy-propyl cyclodextrin, because it is well known in the art to modify the structure of naturally occurring cyclodextrins to obtain cyclodextrin derivatives exhibiting more desirable solubility properties and to stabilize active agents combined with the cyclodextrins. An ordinary skilled artisan would also have been motivated to utilize a peracylated cyclodextrin derivative, such as any one of those taught by Uekama, because these cyclodextrin derivatives can be used to prepare prolonged release drug formulations. It would be desirable to administer a prolonged release drug formulation in the instances, wherein the typical drug dosing regimens requires several daily administrations. A prolonged release dose would require the patient to remember fewer dosing events per day and would reasonably be expected to enhance patient compliance with pharmacotherapy. An ordinary skilled artisan would have had a reasonable expectation of obtaining HFA/drug/acylated drug formulations, because HFA/drug/hydroxypropyl cyclodextrin/drug formulations are known to be suitable and both hydroxypropyl cyclodextrin and the acylated cyclodextrins tested by Uekama are soluble in ethanol. Regarding claim 3 and the recitation of a solution, although Muller's end formulation is a suspension formulation, it is the Examiner's position that an ordinary skilled artisan would readily expect that solution formulations can be obtained by the addition of more solvent (i.e. ethanol). Therefore, the recitation of a solution formulation is considered to be prima facie obvious.

Regarding claim 7, Muller exemplifies a HFA formulation comprising both budesonide and formoterol fumarate dihydrate (Example 5: [0036]) and also teaches that combinations of

active agents are suitable ([0022] and claim 3). Thus, it would have been prima facie obvious to prepare HFA formulations comprising (i) budesonide, (ii) formoterol fumarate dihydrate, and (iii) acylated cyclodextrins. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 2/01/2010 have been fully considered but they are not persuasive. Applicant traverses the instant rejection by attacking the references individually and arguing that (i) the cited references only teach the isolated components and fail to provide any motivation to modify Muller to utilize hydrophobic partially or fully acylated cyclodextrins and (ii) there is no disclosure of acylated cyclodextrins in Muller and Uekema does not teach the inhalation administration of acylated cyclodextrins.

The Examiner respectfully disagrees with and/or finds Applicant's traversal arguments unpersuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The motivation to modify the teachings of Muller to utilize acylated cyclodextrins stems from the prior teachings that acylated cyclodextrins are known to enhance drug solubility in ethanol, impart drug controlled release, and are suitable for administration via a variety of conventional pharmaceutical routes. The fact that Uekema does not explicitly identify inhalation administration as one of the routes of

administration for acylated cyclodextrins is not a fatal flaw, because the prior art recognizes that cyclodextrins can be administered by inhalation. Furthermore, there is nothing in the prior art or of record that would discourage the ordinary skilled artisan from including acylated cyclodextrins in an inhalable formulation or would lead the ordinary skilled artisan to conclude that acylated cyclodextrins are not compatible with inhalation administration. Finally, the teachings of the combined prior art are not required to have the same motivation as Applicant. Thus, the stated motivation for combining the teachings of the cited prior art reference are proper and contrary to Applicant's assertion the rejection is based upon motivation provided by the prior art references. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention. The rejection is maintained.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. García-Marcos ("Inhaled corticosteroids plus long-acting Beta2-agonists as a combined therapy in asthma," *Expert Opinion*, **April 2003**, *4(1)*, pp 23-39) is relevant because it teaches that the combination of betamimetics with inhaled corticosteroids is as effective as the administration of a higher dosage of an inhaled corticosteroid alone.

Claims 1-7 and 11-12 are rejected. Claims 10 and 13 are withdrawn from consideration. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, ~10:00-6:00 and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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